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(54) **Sustained release
microgranules containing sulpiride**

(57) **A controlled release form
constituted by microgranules**

comprising a neutral core provided
with at least one layer containing
sulpiride, when with a second outer
layer constituted by a microporous
envelope containing at least one
natural and/or synthetic polymer.

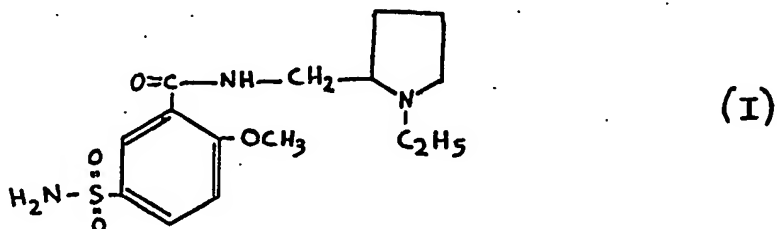
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SPECIFICATION

Novel galenic form of sulpiride, process for its preparation and medicament comprising said novel form

The present invention relates to a novel galenic form of sulpiride, its process of preparation and to a medicament comprising this novel form.

Sulpiride or N-[(ethyl-1-pyrrolidinyl-2)methyl] methoxy-2-sulfamoyl-5-benzamide of the developed formula



has been known for many years and widely used on account of its remarkable pharmacological properties. Thus, it finds use at present both for the treatment of ulcerous and gastro-duodenal disorders (dyspepsia, gastro-duodenal and biliary dyskinesias, chronic gastritis), in psychopathology depressive state of various etiology, schizophrenia) as well as in pediatrics.

However, the administration of sulpiride in its present forms (injectable or drinkable solutions, gelatin capsules, tablets) has notable drawbacks limiting convenience of use.

Among the drawbacks, should be mentioned: — the disadvantage of causing certain intolerances, particularly gastric, which prevent the use of this excellent spasmolytic agent by an important category of patients on the one hand, and on the other hand, which limit its use for long-term treatment;

— the disadvantage of necessitating a plurality of daily doses which cause a rapid succession of increase and decreases of the plasma levels, the organism being subject to overdoses and to underdoses.

Now, the overdosage may even have a serious disadvantage which could be manifested by a dyskinetic crisis of the type of spasmodic torticollis, protrusion of the tongue and trismus.

It is consequently an object of the present invention to provide a novel galenic form of sulpiride which responds better to the necessities of practice than the previously known galenic forms, particularly in that it enables the administered doses of sulpiride to be reduced and thus renders possible prolonged administrations with a single daily dose without causing either overdoses or underdoses.

According to the present invention there is provided a novel galenic form of sulpiride with controlled and programmed release characterised in that it is constituted by microgranules comprising a neutral core constituted by a grain of an inert excipient comprising at least two components of the type belonging to the class constituted by saccharose, starch, talc, drying silica, lactose and stearic acid, this neutral grain being provided with at least one layer comprising sulpiride, then a second outer layer constituted by a microporous envelope comprising at least one natural and/or synthetic polymer belonging to the class constituted by gum lac, gum arabic, gelatin, ethyl cellulose, cellulose acetophthalate, cellulose triacetate, polyoxyethyleneglycol, methacrylates, styrene-acrylonitrile copolymer and polyvinylpyrrolidone in successive envelopes.

According to an advantageous embodiment of the invention, the microporous envelope is formed of gum lac (in a proportion comprised between 1 and 10%), the inert excipient is constituted by a saccharose-starch mixture (in a proportion of 40—80% by weight of saccharose and 10 to 40% by weight of starch) and the sulpiride layer comprises from 1 to 20% by weight of sulpiride, from 0.01 to 0.5% by weight of stearic acid, from 5 to 15% by weight of talc and 2 to 10% by weight of drying silica.

According to another advantageous embodiment of the invention, the neutral core contains also the sulpiride absorbates.

It is also an object of the present invention to provide a process for obtaining the novel galenic form of sulpiride, characterised in that first of all neutral sifted and dried microgranules are prepared, on this central core a sulpiride solution is sprayed, said microgranules are then coated with a suitable coating and the microporous envelope is then formed.

According to an advantageous embodiment of the process according to the present invention, the sulpiride is sprayed onto the neutral core in the form of an alcoholic solution.

According to another advantageous embodiment of the invention, the sulpiride forms a plurality of layers each coated with a different or identical coating layer.

The present invention relates in addition to medicaments constituted by or comprising the novel galenic form of sulpiride.

According to the invention, the medicaments are constituted by a mixture of active microgranules with neutral microgranules.

This principle of mixing microgranules containing the sulpiride with neutral microgranules enables the obtaining of medicaments with a precise and predetermined concentration of sulpiride. The medicaments so obtained may be presented in the form of gelatine capsules, tablets, suppositories, syrups, granules or powder.

5 Beside the foregoing features, the invention comprises still other features which will emerge from the description which follows with reference to an example of the preparation of the medicament according to the present invention as well as to a pharmacological report which establishes the novel properties of the controlled release galenic form according to the present invention. 5

10 It must be well understood, however, that the example of reduction to practise which will be described below, in the same way as the pharmacological report are given purely by way of illustration of the invention but do not constitute a limitation thereof in any way. 10

1. Example of the preparation of the novel galenic form

The example of manufacture corresponds to 100,000 gelatine capsules dosed with 200 mg of sulpiride.

15 a) Manufacturing formula 15

	— sulpiride	20	kg	
	— saccharose	5.2	kg	
	— corn starch	2.8	kg	
	— stearic acid	0.015	kg	
20	— gum lac	0.09	kg	20
	— methacrylic polymers	0.34	kg	
	— talc	0.35	kg	
	— polyvidone	0.80	kg	
25	— acetone and absolute ethyl alcohol:	qsp for 100,000 doses of about 320 mg.		25

b) Process of preparation

The corn starch and saccharose are granulated then sifted and the grains are turbinated for a long time so as to render them perfectly spherical; they are again sifted and fully dried. In a mixer of stainless steel the neutral cores thus obtained are sprayed with an alcoholic solution of sulpiride. Then the first layer is formed by incorporating with these microgranules the other excipients with the exception of the gum lac, and the spraying of sulpiride is recommenced, this coating being repeated several times with sifting and drying if necessary between each layer. 30

35 When the layer containing the active principle is finished, the microporous outerlayer is formed by spraying onto the granules, the gum lac in solution in absolute ethyl alcohol. 35

It is carefully dried removing the remaining ethyl alcohol, again sifted and the titer of the microgranules obtained is checked before placing, for example, in capsules (after having adjusted if necessary the titration by addition and homogenisation with neutral microgranules to arrive at the desired titration of 200 mg of sulpiride par capsule.

40 2. Measurement of the release of the sulpiride 40

The micro-porous outer envelope is formed so as to permit a theoretical prolonged release of sulpiride:

— 1st hour : release less than or equal to 60%

— 4th hour : release less than or equal to 90%

45 — 8th hour : release higher than 95%. 45

To check this characteristic, a disintegration apparatus is used in which a quantity of microgranules corresponding to about 50 mg of active principle are placed in contact with artificial liquids, the apparatus enabling constant stirring to be maintained and the constant temperature of $37^{\circ} \pm 0.5^{\circ}\text{C}$. The artificial liquids are solutions buffered to successive pHs used according to the following scheme: 50

Solutions	Release Time	pH	Results Theoretical—Actual	
25 ml gastric liquid	1 hr (1st hour)	1.5	60%	56%
25 ml intestinal liquid	1 hr (2nd hour)	4.5	60%	
25 ml intestinal liquid	2 hr (3 & 4th hour)	6.9	90%	80.8%
25 ml intestinal liquid	2 hr (5 & 6th hour)	6.9	90%	
25 ml intestinal liquid	2 hr (7 & 8th hour)	7.2	95%	97.3%

Pharmacological Report

- The novel galenic form according to the invention was the subject of a pharmacokinetic study in comparison with the conventional tablet form. The study was carried out in a cross-over test on man.
- 5 Six subjects of male sex received each of the 2 forms into at 2 weeks interval, a capsule of 200 mg of actif principle containing the microgranules and 1 tablet with 200 mg of the conventional form. 5
- The determination of the plasmatic concentration of the sulpiride was carried out by means of 10 samplings in the interval of 72 hours.
- 10 These veinous samplings were of 10 ml and they were carried out at times of 0.5—1—2—3—4—11—16—24—48—72 hours after the taking of the product. 10
- Five ml were centrifuged and the plasma so obtained was transferred into previously silanised test-tubes. These test-tubes were rinsed with a 3% diméthyl-dichlorosilane solution toluene and then heated for two hours at 120°. The plasma was kept in these test-tubes at — 20° before the quantification procedure.
- 15 The quantification of the sulpiride was carried out by high pressure chromatography and electrochemical detection. A specimen of 1 ml supplemented with the internal standard was injected into a chromatographic column (4 cm x 4 mm ϕ) containing Amberlite XAD-2 resin. 15
- This first procedure enables the extract of the sulpiride and the removal, particularly, of the plasmatic proteins. The sulpiride retained in the column was extracted by a méthanol gradient with controlled Ph. The sulpiride and the internal standard were eluted in a fraction of 3 ml of a mixture with 20 60% methanol/water. 20
- After evaporation, the products were taken up again by 90 μ l of water and 40 μ l were injected by means of an injection loop onto a high pressure chromatography column RP—18 (12 cm x 4 mm ϕ int.).
- 25 The elution solvent was constituted by 28% of methanol and 14% of acetonitrile in a phosphate buffer of 0.05 M at pH 7.98, at a flow rate of 1 ml/min. for a pressure of 180 kg/cm² (VARAIN LC 4100 chromatograph). 25
- The detection was carried out by an electro-chemical device with a positive potential of 0.950 volts. The retention time was 3 minutes for the internal standard and of 4.50 minutes for the sulpiride.
- 30 The quantification of the present products was carried out by calculation of the ratio of the height of the peak of the sulpiride and of that of the peak of the internal standard. 30
- At the end of the study, the conclusions were as follows:
- the relative bioavailability is not modified significantly;
 - the time of appearance of the seric peak passes from 2 hours to 4 hours and a half.;
 - the half-life span passes from about 8 hours to more than 12 h
- 35 Study of the curves obtained shows that a capsule with 200 mg is equivalent to almost 2 tablets of 200 mg. 35
- The toxicological study carried out on the rat enabled the 50% lethal dose to be determined when the microgranules were administered orally.
- 40 — in females, the mortality was 40% at 10 g/kg; 40
- in males, the mortality was 40% at 20 g/kg.
- On the clinical level, the tolerance of the novel presentation has been very good and greater than the conventional presentation. It enables thus the practising of treatments of long duration without notable inconvenience for the patient.
- 45 In addition, due to the fact of the economy of 35 to 50% in dosage of active principle, a distinctly improved therapeutic utilisation is thus obtained. 45
- It results from the foregoing description that whatever the method of practice, the embodiment and uses adopted, a novel galenic form of sulpiride is obtained which presents with respect to previously known forms important advantages other than those which have been already mentioned in the foregoing, and particularly:
- 50 50

— it enables a release of the sulpiride to be ensured in a controlled manner and independently of the manner in which the microgranules are administered with a release curve of the active principle constant from one patient to the next and from one administration to the next;

- it permits capsulation and ensures the stability of the sulpiride, which constitutes an important industrial and medical improvement.

CLAIMS

1. Novel galenic form of sulpiride with controlled and programmed release, said form being constituted by microgranules comprising a neutral core constituted by a grain of an inert excipient comprising at least two components of the type belonging to the class constituted by saccharose, starch, talc, drying silica, lactose and stearic acid, this neutral grain being provided with at least one layer comprising sulpiride, then a second outer layer constituted by a microporous envelope comprising at least one natural and/or synthetic polymer belonging to the class constituted by gum lac, gum arabic, gelatin, ethyl cellulose, cellulose acetophthalate, cellulose triacetate, polyoxyethyleneglycol, methacrylates, styreneacrylonitrile copolymer and polyvinyl-pyrrolidone in successive envelopes.
2. Novel galenic form of sulpiride according to claim 1 wherein a microporous envelope is formed from gum lac in a proportion by weight comprised between 1 and 10%.
3. Novel galenic form of sulpiride according to claim 1 or 2, wherein the inert excipient of the neutral core is a mixture comprising from 40 to 80% by weight of saccharose and from 10 to 40% by weight of starch.
4. Novel form according to any preceding claim wherein the sulpridic layer comprises from 1 to 20% by weight of sulpiride, from 0.01 to 0.5% by weight of stearic acid, 5 to 15% by weight of talc.
5. Novel form according to any preceding claim wherein the neutral core comprises sulpiride absorbates.
6. Process for producing the novel galenic form of sulpiride according to any preceding claim, said process comprising preparing first sifted and dried microgranules, spraying onto this neutral core a sulpiride solution, then coating said microgranules by a suitable coating and then forming the microporous envelope.
7. Process according to claim 6, wherein sulpiride is spread onto the neutral core in the form of an alcoholic solution.
8. Process according to claim 6 or 7 wherein sulpiride forms a plurality of layers each covered by different or identical coating layer.
9. Medicaments constituted by or comprising the novel galenic form of sulpiride, according to any one of claims 1 to 5.
10. Medicaments according to claim 9, constituted by a mixture of active microgranules with neutral microgranules.